Intraoperative electroencephalographic burst suppression may help to identify patients at risk for long-term adverse outcome: Findings from a homozygous twins case

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Case report

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Abstract

Background: Postoperative cognitive dysfunction (POCD) presents a risk factor after general anesthesia, especially for old or cognitively impaired patients. Hence, strategies to identify possible patients at risk could help to decrease the rate of POCD. In this case report we relate the occurrence of electroencephalographic burst suppression and low bispectral indices to the development of neurocognitive decline after 12 months in one homozygous twin, whereas the other twin exhibited neither burst suppression nor neurocognitive decline. Case presentation: Two 68-year-old homozygous twins underwent the same surgical procedure with the same anesthetic regimens in comparable concentrations. For cognitive assessment, we applied a battery of neurocognitive tests at baseline (one day before surgery), at hospital discharge (three days after surgery), and 12 months after the procedure. The twins performed similarly in preoperative and discharge testing, but one twin showed worse test performance after 12 months. During surgery, we tested for possible connected consciousness by applying the isolated forearm technique (IFT). For assessment of the level of anesthesia and visual inspection of the EEG, we used the bispectral index (BIS). Neither of the twins showed signs of connected consciousness during anesthesia and the emergence tone to the return of a positive IFT response were similar. We observed lower intraoperative BIS indices for one twin. Furthermore, this twin also had two episodes of Burst Supppression. Vital parameters, particularly mean blood pressure, were stable and comparable during the entire duration of anaesthesia. The twin who exhibited Burst Suppression and lower BIS indices showed distinctly worse cognitive test scores after 12 months compared to baseline and discharge testing, indicating serious neurocognitive decline. The other twin's cognitive performance did not decrease. Conclusions: We present findings from a unique scenario of homozygous twins with comparable lifestyles undergoing the same surgical intervention. The twin with neurocognitive decline had lower BIS values and multiple episodes of BSupp. These findings suggest that EEG monitoring under general anesthesia could help to identify frail brains that may be at increased risk of developing cognitive impairments.

Background

Over the next years, the number of senior patients and patients with cognitive impairments will increase drastically. As a consequence, the number of patients with neurocognitive impairments after anaesthesia will increase as well.[1] In order to develop strategies that can help to minimize these adverse outcomes, intraoperative electroencephalographic (EEG) monitoring could prove helpful. [2] The prevention of very low EEG-based monitoring indices, such as the bispectral index (BIS, Covidien, Boulder CO) and burst suppression (BSupp) patterns, represents an especially promising approach. In fact, deep hypnotic levels represented by low indices and/or BSupp have been independently associated with postoperative mortality,[3-5] but their influence on postoperative cognitive dysfunction (POCD) and delirium (POD) has not been established.[6-7] Episodes of BSupp have also been associated with delirium in the postoperative area unit[8] and POD.[9-10] In general, the relationship between deep anaesthesia (with BSupp) and outcome is still a matter of controversial discussion.

In addition to the consequences of excessively deep sedation, anaesthesia of inadequate depth could trigger intraoperative awareness events[11] that could also lead to long-tern neurocognitive decline because of post-traumatic consequences.[12]

Here we present a case of senior homozygous twins with similar lifestyle that underwent the same surgical intervention, with one twin developing postoperative cognitive dysfunction. We evaluated intraoperative BIS values, visually-identified BSupp episodes, vital parameters, and drug concentrations to find a possible anaesthesia-related explanation for the differences in outcome between the brothers.

Case Presentation

We present the case of two Italian 68-year-old male homozygous twins (S1 and S2) who underwent general anaesthesia for total thyroidectomy. The twins have the same level of education (5 years in school), and both worked as blacksmiths and lived on different floors in the same house with their families. Their weight and height were similar as well: 73 kg and 174 cm (S1) and 76 kg and 175 cm (S2). Both twins had essential hypertension that was well controlled with beta-blockers. Prior to this intervention, neither of the brothers had undergone surgery or received general anaesthesia.

Procedure

For thyroidectomy, the procedures for each twin were similar. Neither received premedication, and anaesthesia was induced with fentanyl 150 mcg and propofol 2 mg kg^{-1}. For neuromuscular blockade (NMB), we delivered 1 mg kg^{-1} of rocuronium. After orotracheal intubation, we maintained anesthesia with desflurane at a minimum alveolar concentration (MAC) of 0.8 (5.4% vaporizer setting on the Dräger Zeus® Infinity® Empowered anaesthesia machine). We further administered two fentanyl boluses: 150 mcg just before skin incision and 100 mcg 40 minutes later. We also gave rocuronium boluses of 0.15 mg kg-1 to maintain a deep NMB, defined as absence of first twitch at train-of-four stimulation. Thirty minutes before the end of surgery, the patients received paracetamol 1000 mg, ketoprofen 160 mg, and ondansetron 4 mg for pain, nausea and vomiting prophylaxis, respectively. At the end of surgery, we reversed the deep NMB with sugammadex (4 mg kg^{-1}) and discontinued desflurane delivery.

Monitoring

We monitored level of anaesthesia in both twins with a BIS monitor by applying a BIS Quatro Sensor to the forehead. The display of the raw EEG on the BIS monitor also allowed for visual inspection for intraoperative BSupp episodes. We applied the isolated forearm technique (IFT) to test for possible episodes of connected consciousness and conducted a train-of-four monitoring using the TOF-watch SX (Organon, Ireland) to assess the state of NMB. We attached BIS and the TOF-watch monitors before anaesthesia induction according to the manufacturer specification and removed them after anaesthesia emergence. We placed the tourniquet for IFT monitoring on the dominant (right) arm before induction. It was inflated after injection of propofol and fentanyl, but before the patients received rocuronium. We

deflated the tourniquet only after complete reversal of NMB (verified by TOF) at the end of surgery. We performed IFT testing at 5-minute intervals throughout surgery. To facilitate this, each patient wore headphones through which the following prerecorded voice message was played: "*Name, name, it's your anaesthesiologist speaking. If you can hear me, squeeze your hand*… [10 seconds pause] … *Name, name, it's your anaesthesiologist speaking. If you feel pain, squeeze your hand twice*" (with "name" replaced by the name of the patient). All data was collected using paper data collection form.

Cognitive assessment

Both twins underwent the same neuropsychological tests at three different times: the day before surgery (T0), 3 days after surgery (T1), and 12 months after surgery (follow-up). We performed (i) Montreal Cognitive Assessment (MoCA), (ii) Trail Making Test A (TMT-A) and B (TMT-B), (iii) Forward and Backward Digit Span Tests (DST), and (iv) the Frontal Assessment Battery (FAB). These tests are designed to assess cognitive function, including short-term memory, working memory, visuo-spatial research ability, selective and divided attention, psychomotor speed and executive functions. After correcting the scores for age and level of schooling, a psychologist (APM) interpreted the results. We considered both cut-off values (26/30 for MoCA, 94 seconds for TMT-A, 283 seconds for TMT-B, 3.75/9 for DST Forward, and 3/9 for DST Backward) as well as z-scores (for FAB) for the evaluation of cognitive status. Cognitive deficit was defined as a score below the cut-off value for the MoCA test and DST, a score above the cut-off for the TMT tests, or a z-score of at least –1.0 for the FAB test (i.e., a reduction of one or more standard deviations in FAB performance). We further assessed the level of sedation during anaesthesia emergence with the Richmond Agitation-Sedation Scale-RASS. [13]

Results

Neither twin required vasoconstrictor drugs during general anaesthesia, as their intraoperative haemodynamic parameters were stable. Neither twin reported explicit recall. The duration of surgery was very similar (77 minutes for S1 and 84 for S2).

Monitoring results

Before induction of anaesthesia, the BIS values for S1 and S2 were 97 and 98, respectively. The mean BIS values during maintenance phase were 35 for S1 and 42 for S2. Furthermore, we visually identified two episodes of BSupp in patient S1: the first episode occurred after skin incision and lasted 12 minutes, and the second occurred approximately 40 minutes after skin incision (after the 100 mcg fentanyl bolus) and lasted 8 minutes. No BSupp was observed for S2. Intraoperative BIS values are summarized in Table 1.

Neither patient exhibited a positive IFT response during surgery. S1 had a positive response 8 minutes after discontinuing desflurane and was extubated 3 minutes later. He was confused (Richmond Agitation-Sedation Scale-RASS: -2) for approximately 10 minutes after awakening. S2 had a positive IFT response 6 minutes after discontinuing desflurane and was extubated 4 minutes later. He was confused (RASS: -3)

for approximately 5 minutes after awakening. Neither patient exhibited arm complications related to ischemia induced by the tourniquet.

Intraoperative monitoring values during surgery are shown in Table 1.

Neurocognitive testing results

Preoperatively, scores obtained at MoCA, FAB tests and Backward DST fulfilled the definition of (mild) cognitive deficit for both twins. 3 days after the operation, all test scores were worse compared to the pre-op tests in both twins, except for the Forward and Backward DST scores which remained the same. The scores were similar between the brothers for these assessments. At the 12-month follow-up, the neurocognitive test results for S2 were similar to his postoperative results. S1, in contrast performed worse in all tests. All scores fulfilled (or almost fulfilled [TMT-A score was at the cut-off value]) the definition of neuro-cognitive dysfunction.

Neurocognitive test results are shown in Table 1.

Table 1: Neurocognitive test results and intraoperative monitoring values.

BIS: bispectral index; DST: Digit Span Test; FAB: Frontal Assessment Battery; IFT: isolated forearm technique; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test. Neurocognitive results in parentheses (c) represent age- and schooling-corrected values.

TWIN	PRE-OPERATIVE NEUROPHYSIOLOGICAL TESTS (1day before surgery)																			
	MoCA (c)			TMT-A (c)			TMT-B (c)			FAB (c) [z-score]						DST Forward (c) & DST Backward (c)				
S1	22	(23)		59		(35)	124		(37)	12		(13)	[-1,38]			4	(4,5)	&	2	(2)
S2	23	(24)		57		(33)	128		(41)	12	(13)		[-1,38]			4	(4,5)	&	2	(2)

	INTRA-OPERATIVE MONITORING			
	Induction phase		Induction-Incision phase		Surgical phase	
	Mean BIS (n)	IFT responses (n)	Mean BIS (n)	IFT responses (n)	Mean BIS (n)	IFT responses (n)
S1	32	0	40	0	33	0
S2	39	0	46	0	42	0

	POST-OPERATIVE NEUROPHYSIOLOGICAL TESTS (3 days after surgery)																			
	MoCA (c)			TMT-A (c)			TMT-B (c)			FAB (c) [z-score]						DST Forward (c) & DST Backward (c)				
S1	20	(21)		62		(38)	125		(38)	10		(11)	[-2,92]			4	(4,5)	&	2	(2)
S2	19	(20)		60		(36)	130		(43)	11		(12)	[-2,15]			4	(4,5)	&	2	(2)

	FOLLOW-UP NEUROPHYSIOLOGICAL TESTS (12 months after surgery)																			
	MoCA (c)			TMT-A (c)			TMT-B (c)			FAB (c) [z-score]						DST Forward (c) & DST Backward (c)				
S1	12	(13)		94		(70)	Unable (-)			6	(7)		[-6]			2	(2,5)	&	1	(1)
S2	22	(23)		61		(37)	135		(48)	11		(12)	[-2,15]			4	(4,5)	&	2	(2)

Discussion And Conclusions

In this case report we describe two patients, homozygous twins, who had the same medical history, and received the same anaesthesia regimen for the same surgical intervention (total thyroidectomy). The intervention duration was similar, as were the vital parameters (particularly the lack of hypertension). The brothers did not have excessively light levels of general anaesthesia, i.e., no connected consciousness as tested with IFT. They also had similar perioperative and postoperative (3 days) neurocognitive test results. Nevertheless, S1 performed substantially worse in neurocognitive tests one year after surgery. Short-term memory, working memory, and frontal functions (conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, environmental autonomy) were most affected.

We observed lower BIS values and episodes of BSupp in S1, but not in S2. Since low BIS and BSupp seem associated with a higher risk of adverse outcomes,[3-5, 8-10] our finding may present an unmasking of a frail brain.

The cognitive decline of S1 after 12 months was not predicted by any of the peri-operative tests. Both twins performed in a similar fashion before surgery and in the 3-day postop test.

In our opinion, given that these two homozygous twins underwent the same surgical procedure and anaesthesia protocol, the fact that only the one with BSupp had a worse 12-months outcome suggests that his brain was more susceptible to anaesthetic drugs than the other's. This could mean that the generation of BSupp may have unmasked the more fragile brain of S1, even if there was no development of cognitive impairment at the first days following general anaesthesia.

Besides the unique opportunity to observe the postoperative cognitive function, the brothers presented a risk patient group for an adverse cognitive outcome. They were of older age (>65 years), received limited education, and showed signs of mild cognitive impairment before surgery.[1] Despite this, only one brother - the one with BSupp - developed POCD. Hence, our result may also point towards the necessity of longer follow-up periods for patients at risk. Also, BSupp did not occur in situations of hypotension that would have made our case a triple low case[14]. In the current state of the literature where the role of Bsupp and neurocognitive outcome is still debated,[6-7] our case report suggests a possible association between low BIS/BSupp and long-lasting neurocognitive consequences.

Of course, our observation is just a case report and is significantly limited by the lack of additional neuropsychological follow-up evaluations in the postoperative period closer to surgery as well as later on. However, 18 months after surgery, S2 has continued living at home while S1 had to be transferred to a long-term-stay hospital for elderly. Furthermore, our BIS and EEG data were only observational and were assessed by visual inspection. Hence, we cannot compare the data of these patients to those of other subjects.

In conclusion, we would like to state that our observation shows the potential of intraoperative BSupp identification in helping to unmask a frail brain at risk for (long-term) cognitive impairments.

List Of Abbreviations

IFT: Isolated forearm technique

BIS: Bispectral Index

BSupp: Burst Suppression

POD: Postoperative delirium

POCD: Postoperative cognitive dysfunction

MAP: Mean arterial pressure

NMB: neuromuscular blockade

TOF: train-of-four

MoCA: Montreal Cognitive Assessment

TMT: Trail Making Test

DST: Digit Span Test

FAB: Frontal Assessment Battery

RASS: Richmond Agitation-Sedation Scale

Declarations

Ethical approval and consent to participate

Both patients (S1 and S2) provided written informed consent for participation in this case report. Ethical approval was not applicable since the monitoring and treatments of patients involved did not differ from routine clinical practice at our hospital.

Consent to publish

Written informed consent was obtained from the participants for publication of this article and any accompanying tables/images.

Availability of data and materials

This case report contains clinical data from medical records in our hospital. All the relevant data for this case-report, reported anonymously, have been inserted in the Table 1.

The datasets used in this current case-report, as well as the signed consent to participate and consent to publish, are available from the corresponding author upon reasonable request.

Competing interests

There are no competing nor financial interests.

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Author's contributions:

FL and PZ conceived of the study; acquired, collected, and analysed data; and drafted and revised the final manuscript. APM, EM and ER collected and analysed data, and revised the final manuscript. MK participated in analysing the data, discussing the results, and revising the final manuscript. MC participated in conceiving the study, analysing the data, discussing the results, and revising the final manuscript. All authors read and approved the manuscript.

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